

Introduction

Active tuberculosis (TB) is a serious co-morbidity for children with severe acute malnutrition (SAM) in TB-endemic settings. TB diagnosis is particularly challenging in children, and largely based on clinical symptoms. Children rarely produce sputum and invasive specimen-collection procedures often have poor yield. The TB LAM test (Determine™) is a lateral-flow strip-test, which detects mycobacterial lipoarabinomannan (LAM) antigen in urine. The test has shown diagnostic value for TB-screening among immunocompromised HIV-positive adults. No data exist for SAM children.

Methods

Study design: Cross-sectional assessment

Eligibility criteria

- SAM diagnosed
- hospitalized
- <5 years old
- not on TB treatment
- Informed consent provided by caretaker

Group 1: at least 1 symptom suggestive of TB:

- Contact with known or presumed TB case
- Poor weight gain despite appropriate nutritional support
- Persistent pneumonia after appropriate, well-monitored antibiotic treatment
- Persistent cough
- Persistent fever for > 1 week after excluding common causes
- Persistent or worsening fatigue
- Chest Xray suggestive of TB

Group 2: without any symptoms suggestive of TB

Sample size: N=100 each group

Primary objectives:

- To estimate the percentage of LAM test-positive among children hospitalised with SAM with or without suspicion of TB, respectively.
- To describe the clinical and TB-diagnostic characteristics of LAM-test positive and LAM-test negative children, respectively.

Study site

In-patient facility of the intensive nutrition center (Centre de Récupération Nutritionnelle Intensive, CRENI) supported by Médecins Sans Frontières (MSF) in Madaoua district, Tahoua Region, Niger.

Programmatic TB diagnosis

Hospitalized SAM children were routinely screened for TB, mainly based on clinical symptoms, sometimes chest-Xray was done (external), rarely Ziehl-Neelsen microscopy due to challenges with sample collection. No access to TB culture. GenXpert TB molecular test using naso-pharyngeal aspirations was not available during most of the study period. All children were tested for HIV (rapid test). Programmatic clinical- and diagnostic data were collected during hospitalisation for each included child.

TB-LAM test

Hospitalised children with or without symptoms of TB, respectively, were included consecutively until sample size was reached. One urine specimen was collected for each child at study inclusion, using collection pots or urine bags. LAM-test (4-grade reading scale) was performed in the laboratory with 60µL unprocessed urine on the day of urine collection, following manufacturer's instructions. LAM results remained blinded to clinical staff and were not used for patient management.

Data analysis: Frequencies were compared with chi-square test and median compared by with Wilcoxon rank-sum test, analysis with Stata software (13).

Ethical approval: The study received approval by the Comité Consultative National d'Éthique, Niamey, Niger, and the MSF Ethics Review Board.

Results

Group-1: N=103 children included between February 2016-February 2017.

Table 1: Characteristics of group-1 (with symptoms suggestive of TB)

	All	LAM-negative	LAM-positive	p-value
Total included, N (%)	* 102 (100)	49 (48)	53 (52)	-
Age, months, median (IQR)	19 (11 -24)	23 (11-24)	18 (10-24)	0.22
Female	52 (51)	22 (45)	30 (57)	0.24
Z-score -3 or -4	# 96 (95)	46 (94)	50 (96)	0.59
Bilateral Oedeme	7 (7)	3 (6)	4 (8)	0.78
HIV sero-positive	## 2/101 (2)	1 (2)	1 (2)	0.63
Median Days of hospitalization, (IQR)	13 (9-17)	12 (9-17)	13 (9-18)	0.59
Symptoms suggestive of TB at inclusion				
Persistent cough ≥ 2 weeks	70 (69)	32 (65)	38 (72)	0.49
Unexplained fever > 1 week	# 48 (48)	23 (47)	25 (48)	0.9
Persistent pneumonia (after antibiotics)	66/95 (69)	31 (69)	35 (70)	0.9
Poor weight gain despite nutritional support	45/95 (47)	25 (56)	20 (40)	0.13
Persistent or worsening fatigue	45/95 (47)	22 (49)	23 (46)	0.78
Contact with person diagnosed with TB	15 (15)	3 (6)	12 (22)	0.02
Suspected extra-pulmonary TB	4 (4)	2 (4)	2 (4)	0.95
TB Diagnostics (programmatics)				
Chest Xray suggestive of TB (among tested)	19/43 (44)	10 (56)	9 (36)	0.20
GenXpert MTB detected (among tested)	2/7 (29)	1 (33)	1 (25)	0.81
Main diagnoses at dis-charge (non-exclusive)				
TB (started on treatment)	22 (22)	8 (16)	14 (26)	0.22
Respiratory infection	76 (75)	37 (76)	39 (74)	0.82
Anemia	63 (62)	30 (61)	33 (62)	0.91
Sepsis	31 (31)	15 (31)	16 (30)	0.96
Diarrhoea	23 (23)	10 (20)	13 (25)	0.62
Malaria	21 (21)	9 (18)	12 (23)	0.59
Outcome at discharge				
Transferred to ambulatory nutrition center	81 (80)	38 (78)	43 (81)	
Died	20 (20)	10 (20)	10 (19)	0.56
Lost-to-follow up	1 (1)	1 (2)	0	

* n=1 excluded (LAM-test result undetermined); # n=1 missing; ## n=1 discordant, n=1 not tested

Characteristics of group-2 (no symptoms suggestive of TB) (not tabulated):

- N=100 children included between January-August 2017.
- Median Days of hospitalization: 5.5 (IQR:4, 9.5).
- 29% female, median age 16 months (IQR: 10-24), significantly lower among LAM-positive (11.5; IQR: 9-19) than LAM-negative (18; 11.5-24) (p=0.009).
- None was a known contact of a person diagnosed with TB.
- None diagnosed with TB.
- Main diagnoses recorded (non-exclusive): 58% diarrhoea, 40% malaria, 23% anemia, 21% marasm, 9% kwashiorkor, 7% respiratory infection, 2 % sepsis.
- No death reported, all children transferred to ambulatory nutrition center.

Table 2: LAM test results by group

	Group-1			Group-2
	with symptoms suggestive of TB			without any TB symptom
	All	Started on TB treatment	Not Started on TB treatment	Not Started on TB treatment
	N=103	N=22	N=81	N=100
LAM negative	49 (48)	8 (36)	41 (51)	64 (64)
LAM positive	53 (52)	14 (64)	39 (48)	36 (36)
grade 1	38/53	9	29	34/36
grade 2	11/53	3	8	1/36
grade 3	4/53	2	2	1/36
grade 4	0	0	0	0
LAM undetermined	1	0	1	0

- High percentage of LAM-positive detected among hospitalised SAM children.
- Higher LAM-positivity in group-1 (**52%**; CI95: 42-62) than in group-2 (**36%**;CI95: 27-46) (p=0.02).
- LAM-band intensity higher than grade 1 was rare, but more frequent in group-1 (28% versus 5.6%) (p=0.008).
- No evidence found for association of LAM-test-positivity (p=0.22) or LAM-grade (p=0.52) with programmatic TB diagnosis (=children started on TB treatment), respectively.

Summary & Discussion

- We found surprisingly high levels of LAM-positivity among children <5 years hospitalised SAM.
- Comparison of LAM-test results with programmatic TB diagnosis suggests poor diagnostic performance of LAM in SAM children presenting with symptoms of TB, indicating that false-positivity may be an issue in this population. This was further supported by more than one third of children presenting without any symptom of TB also testing LAM-positive.
- The vast majority of LAM-positive results were low intensity (grade 1), and no association was found between higher grade LAM intensity and programmatic TB diagnosis.
- On the other hand, the significantly higher proportion of LAM-positivity among children presenting with symptoms suggestive of TB may also indicate some degree of under-diagnosis of TB among hospitalized SAM children.
- This study explored TB-LAM-positivity in the context of programmatic TB diagnosis which was largely based on symptoms and thorax-radiography and has known limitations, especially in this children population.
- Further evaluation of the LAM-test in SAM- and other children patient groups is recommended, including also systematic comparison with other available diagnostic tools for TB.
- Feasible and performant TB diagnostic tests for children are urgently needed.